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Who benefits from additional drug counseling among prescription opioid dependent patients receiving buprenorphine-naloxone and standard medical management?

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Abstract

Background—In the multi-site Prescription Opioid Addiction Treatment Study (POATS), conducted within the National Drug Abuse Clinical Trials Network, participants randomly assigned to receive individual drug counseling in addition to buprenorphine-naloxone and medical management did not have superior opioid use outcomes. However, research with other substance dependent populations shows that subgroups of participants may benefit from a treatment although the entire population does not.

Method—We conducted a secondary analysis of POATS data to determine whether a subgroup of participants benefited from drug counseling in addition to buprenorphine-naloxone and medical management, either due to greater problem severity or more exposure to counseling as a result of greater treatment adherence. Problem severity was measured by a history of heroin use, higher Addiction Severity Index drug composite score, and chronic pain. Adequate treatment adherence was defined a priori as attending at least 60% of all offered sessions.

Results—Patients who had ever used heroin and received drug counseling were more likely to be successful (i.e., abstinent or nearly abstinent from opioids) than heroin users who received medical

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Contributors

Drs. Weiss and Potter designed the study and wrote the protocol. Dr. Dreifuss and Ms. Dodd managed the literature searches and summaries of previous related work. Dr. Griffin undertook the statistical analysis, and Drs. Weiss, Dreifuss, and Griffin and Ms. Dodd wrote the first draft of the manuscript. Drs. Connery and Carroll participated in the conceptualization of the paper and reviewed and critically edited ongoing drafts. All authors contributed to and have approved the final manuscript.

Author Disclosures

Dr. Weiss has consulted to Titan Pharmaceuticals and Reckitt-Benckiser.

management alone, but only if they were adherent to treatment and thus received adequate exposure to counseling (OR=3.7, 95% CI=1.1-11.8, p=0.03). The association between severity and outcome did not vary by treatment condition for chronic pain or ASI drug severity score.

Conclusions—These findings emphasize the importance of treatment adherence, and suggest that patients with prescription opioid dependence are a heterogeneous group, with different optimal treatment strategies for different subgroups.

Keywords

prescription opioids; treatment; counseling

1. INTRODUCTION

Prescription opioid dependence continues to be a significant public health problem in the United States (Substance Abuse and Mental Health Services Administration, 2011). Although research suggests that prescription opioid users differ from heroin users on important prognostic factors (Moore et al., 2007; Sigmon, 2006; Wu et al., 2011) and may have different treatment outcomes (Moore et al., 2007; Nielsen et al., 2013; Potter et al., 2013), most existing studies of opioid dependence treatment have focused primarily on heroin users. To bridge this gap, the Prescription Opioid Addiction Treatment Study (POATS) was conducted as part of the National Drug Abuse Treatment Clinical Trials Network (Weiss et al., 2010). POATS was a multisite, two-phase randomized, controlled trial (N=653) that used buprenorphine-naloxone to treat patients dependent on prescription opioids. All study participants received standard medical management, and half were randomized to receive adjunctive individual opioid dependence counseling. Only 7% of participants met study criteria for successful outcome (i.e., abstinence or near-abstinence from opioids) in the first phase of POATS (a brief buprenorphine-naloxone taper), while 49% were successful at the end of 12 weeks of buprenorphine-naloxone stabilization in the extended treatment phase (Phase 2) of the study. Results showed that additional counseling did not affect treatment outcome in either the brief or the extended treatment phase (Weiss et al., 2011).

Studies of other substance dependent populations have shown that although a treatment may not have an effect on the population as a whole, it may benefit certain subgroups of participants (Anton et al., 2008). Thus, although additional counseling did not improve outcome for the POATS population overall, certain subpopulations of prescription opioid dependent patients receiving buprenorphine-naloxone pharmacotherapy and standard medical management may have benefitted from the additional counseling offered in POATS.

When considering which subgroups of participants might have better outcomes with additional counseling, we focused on two potential sources of variability: 1) participant characteristics and 2) adherence to treatment, resulting in adequate exposure to the intervention. In examining participant characteristics, we examined severity of drug problems, because some previous research has demonstrated that patients with more severe drug problems may benefit from more intensive treatment (Hser et al., 1998; McKay et al.,

2002; Tiet et al., 2007). Although problem severity among individuals with substance use disorders (SUDs) has been defined in a number of ways, including chronicity of dependence (Carroll et al., 1993) and pre-treatment quantity or frequency of drug use (Brewer et al., 1998; Laffaye et al., 2008; Saxon et al., 1996), the Addiction Severity Index (ASI; McLellan et al., 2006) drug composite score is a commonly used, well-validated measure of severity of drug dependence (Crits-Christoph et al., 1999; Farabee et al., 2013; Rosenheck et al., 2011). Additionally, for our study population of individuals dependent on prescription opioids, two other potential markers of response in this population were examined: 1) a lifetime history of heroin use, because of its association with poorer outcome in POATS (Weiss et al., 2011) and 2) chronic pain, due to its high prevalence rate among opioid-dependent individuals (Potter et al., 2008; Rosenblum et al., 2003) and its association with greater severity of SUD symptoms (Rosenblum et al., 2003; Trafton et al., 2004).

In addition to severity, another potential reason for varying effectiveness of a treatment intervention among subgroups of an overall patient population is treatment adherence, resulting in differential exposure to the treatment. Not surprisingly, patients who are adherent to a treatment regimen and thus receive an adequate amount of a treatment intervention are more likely to benefit from it (Fareed et al., 2009; Montoya et al., 2005). Past research has shown that individual and group therapy are more effective for SUD patients who attend more treatment sessions (Fiorentine and Anglin, 1996; Lydecker et al., 2010; Montoya et al., 2005); thus, it is likely that level of attendance of treatment sessions among POATS patients may have been related to treatment outcome among patients who received adjunctive opioid dependence counseling.

We therefore conducted a secondary analysis of data from POATS to determine whether a subgroup of participants benefited from drug counseling in addition to buprenorphine-naloxone and standard medical management, either due to greater problem severity, more exposure to counseling as a result of greater treatment adherence, or the interaction of these variables.

2. METHODS

Data were collected as part of a multi-site, randomized, controlled trial examining different intensities of counseling in the context of different lengths of buprenorphine-naloxone treatment for patients with prescription opioid dependence (for details of the parent study, see Weiss et al., 2011). Treatment-seeking participants met DSM-IV criteria for current opioid dependence, and were at least 18 years of age. Key exclusion criteria included a requirement of ongoing pain management with opioids, currently unstable psychiatric illness, or concurrent formal substance use disorder treatment (other than mutual-help groups; see Weiss et al., 2011 for details).

We included participants with a very limited history of heroin use to increase generalizability of our study results to typical treatment-seeking prescription opioid dependent populations, while ensuring that we were examining a new population of participants who either exclusively or predominantly used prescription opioids. We thus

excluded individuals with heroin use on ≥4 days in the past month, a lifetime diagnosis of opioid dependence due to heroin alone, or a history of ever injecting heroin.

POATS consisted of two phases. In Phase 1 (brief treatment), participants were inducted onto buprenorphine-naloxone, stabilized for two weeks, tapered during the next two weeks, and followed for eight additional weeks. Those who abstained or nearly abstained from opioids during that 12-week period completed the trial as Phase 1 successes. Those who relapsed to opioids were invited to enter Phase 2 of the study (the extended-treatment phase), consisting of 12 weeks of buprenorphine-naloxone, a four-week taper, and an eight-week post-taper follow-up. In each phase, participants were randomized to receive either 1) standard medical management (SMM) alone or 2) SMM plus individual opioid dependence counseling (ODC). In Phase 1, randomization was stratified by 1) presence of lifetime history of heroin use and 2) current chronic pain. In Phase 2, randomization was stratified by Phase 1 treatment condition. At SMM visits, buprenorphine-naloxone was dispensed, and brief medically-oriented counseling was conducted by a buprenorphine-certified physician, who reviewed medication side effects and withdrawal symptoms, and encouraged abstinence, mutual-help group attendance, and medication adherence. SMM visits, which lasted 15-20 minutes, took place twice during the initial week of the extended treatment phase, then weekly for the following 11 weeks. In addition, half the subjects were randomly assigned to receive opioid dependence counseling (ODC) in longer (45-60 minutes) and more frequent visits: twice a week for six weeks, then weekly for six weeks in the extended treatment phase. ODC, conducted by a trained substance abuse or mental health professional, employed relapse prevention strategies, encouraged abstinence, and focused more intensively on high-risk situations and interpersonal stresses. Assignment to additional ODC was not related to outcome in either phase. Because so few participants were successful in Phase 1, this report focuses on the second phase (extended treatment) of the parent study.

2.1 Measures

A series of standardized assessments was administered to all participants. The Composite International Diagnostic Interview was used to diagnose opioid dependence. The Pain and Opiate Analgesic Use History, developed for this study, was administered at baseline to assess opioid use history. Severity of problems was measured by the Addiction Severity Index (ASI) drug composite score, the presence of lifetime heroin use, and the presence of current chronic pain. The ASI (McLellan et al., 2006, 1985) is a widely used, multidimensional interview, which assesses the severity of addiction-related problems. Chronic pain was defined by the Brief Pain Inventory (Keller et al., 2004) as “pain beyond the usual aches and pains, not including withdrawal pain” for at least 3 months.

The Substance Use Report, corroborated by weekly urine drug screens, was administered weekly during treatment and every two weeks during follow-up. This was the primary measure to determine outcome in Phase 2 of the study: “successful outcome” was defined as urine-confirmed self-report of abstinence from opioids during the final week of buprenorphine/naloxone treatment (week 12) and during ≥2 of the 3 weeks prior (weeks 9-11).

For analysis, “adequate adherence,” and thus an adequate “dose” of treatment, was defined at the beginning of the trial as attending at least 60% of offered sessions (see Section 3.2.2 for more details). Although definitions of the level of attendance at which patients can be considered to have completed treatment vary (Najavits et al., 1998; Wolitzky-Taylor et al., 2012), treatment completion has often been defined as between 60% and 80% of sessions attended (Brady et al., 2001; Hien et al., 2012; Outlaw et al., 2012).

2.2 Statistical analysis

Subjects for this report include the 360 patients randomized in Phase 2 of the main study. Chi square tests assessed the associations between dichotomous variables. A series of logistic regression models examined the effects of severity, Phase 2 treatment, treatment adherence, and the interaction between severity and treatment on opioid use outcomes at the end of the 12-week buprenorphine/naloxone treatment, adjusted for the stratification variable, Phase 1 treatment condition.

3. RESULTS

3.1 Sample description (N=360)

Most participants (90.6%) were white and 41.9% were female. Mean age was 32.5 years (sd=9.7), and mean education was 12.9 years (sd=2.2). Half (50.0%) were never married, and most (60.3%) were employed full-time. ASI drug composite scores were high, as expected: mean=.34 (sd=.07) with a range from .08-.54. ASI alcohol composite scores were considerably lower: mean=.05 (sd=.09) ranging from 0-.84 (n=338). About a quarter (26.1%) reported ever having used heroin, and 38.3% reported current chronic pain at study intake.

3.2 Treatment success

There were 653 participants in Phase 1, the short-term buprenorphine/naloxone treatment. At the end of Phase 1, only 6.6% of the participants (n=43) were successful; the remaining participants were invited to enter phase 2, the extended buprenorphine/naloxone treatment. After dropout and refusals, 360 participants entered Phase 2. By design, all 360 participants received SMM and half (n=180) were randomly assigned to also receive ODC. At the end of the 12-week treatment, 177 (49.2%) met criteria for a successful outcome. Treatment condition (i.e., SMM vs. SMM+ODC) was not related to outcome at the end of either Phase 1 or Phase 2 (Weiss et al., 2011).

3.2.1 Question 1: Did participants with more severe problems have better outcomes with SMM+ODC than with SMM alone (N=360)?—Logistic regression models examined the interaction between severity and treatment condition for opioid use outcomes at the end of the 12-week treatment, adjusted for Phase 1 treatment condition (see Table 1a). The association between severity and outcome did not vary by treatment condition for any of the three severity measures. Regardless of treatment condition, as reported previously (Weiss et al., 2011), patients who had never used heroin were more likely to have successful outcomes than patients who had used heroin. The remaining two

measures of severity, ASI drug composite score and chronic pain, were not associated with outcome, regardless of treatment condition.

3.2.2 Question 2: Among participants with adequate adherence to treatment, were those assigned to SMM+ODC more likely to have successful outcomes than those receiving SMM alone, regardless of severity (n=266)?—Treatment attendance was examined, with adequate adherence to treatment defined a priori as attending ≥60% of assigned SMM sessions for all participants and ≥60% of SMM sessions and ≥60% of ODC sessions for participants assigned to the additional counseling condition. Most participants (n=266, 73.9%) attended at least 60% of treatment sessions. Participants assigned to SMM alone were more likely to meet this criterion than those assigned to SMM +ODC (82.2% vs. 65.6%, $\chi^2(1)=12.96$, $p<0.001$); however, adequate adherence to SMM sessions did not differ by treatment condition (82.2% vs. 84.4%, ns). Logistic regression models examined the association between treatment condition and opioid use outcomes at the end of the 12-week treatment, adjusted for Phase 1 treatment condition. Treatment condition (i.e., SMM+ODC vs. SMM alone) was not associated with successful Phase 2 opioid use outcomes (see Table 1b).

3.2.3 Question 3: Among participants with adequate adherence to treatment, were those with more severe problems more likely to succeed with additional counseling than with standard medical management only (n=266)?—Among those participants who attended at least 60% of all assigned sessions, the interaction of severity and treatment condition was examined. Among participants who had ever used heroin, those assigned to SMM+ODC were more likely to succeed than those in SMM only (66.7% vs. 35.0%, n=70, $\chi^2(1)=6.88$, $p=.016$). In contrast, treatment condition was not associated with successful outcomes among participants with adequate adherence who had never used heroin (65.9% vs. 64.8%, n=196, $\chi^2(1)=0.03$, $p=.873$). As a follow-up to this bivariate analysis, a logistic regression model, adjusted for Phase 1 treatment condition, was examined (Table 1b). Results showed that the interaction between severity and Phase 2 treatment condition was significant for heroin, i.e., adherent participants who had ever used heroin were more likely to have a successful opioid outcome in SMM+ODC vs. SMM alone at the end of treatment (relative to participants who had never used heroin). This analysis was repeated for chronic pain and ASI drug composite scores; the interaction of treatment condition with these measures of severity was not associated with outcome.

3.3. Medication dose and adherence

Because of the potential difficulty of demonstrating the effect of counseling when combined with an efficacious medication, we examined dose of buprenorphine/naloxone and level of medication adherence to see if these factors influenced our results. The mean maximum daily dose of buprenorphine/naloxone taken during weeks 1-12 of Phase 2 was 20.3 mg (sd=7.9, n=356). The total dose prescribed ranged from 64 to 2752 mg (0-87 days of treatment, including a 3-day visit window; no participant was prescribed more than 32 mg on any study day), with a mean of 1369.7 (sd=603.6, N=360); the mean level of adherence (i.e., total dose taken/total dose prescribed) was 95.4% (sd=14.9, N=360). The logistic regression models reported above were adjusted for medication adherence and maximum

daily dose. The results were supported; hence, variation in medication dose and adherence did not alter the findings.

4. DISCUSSION

This study employed a secondary analysis of data from the multi-site Prescription Opioid Addiction Treatment Study to determine whether the addition of drug counseling to buprenorphine-naloxone treatment plus standard medical management was related to successful outcomes for a subgroup of prescription opioid-dependent patients. Specifically, this study explored the effects on outcome of the association between treatment condition, severity of addiction problems, and treatment attendance. Patients with a lifetime history of heroin use who received additional drug counseling were more likely to succeed than heroin users who received standard medical management alone, but only if they were adherent to treatment and thus had adequate exposure to counseling. The interaction of treatment condition with chronic pain and with ASI drug severity score was not associated with outcome.

Overall, there was no effect of additional drug counseling in POATS, and prescription opioid-dependent patients with a history of heroin use had poorer treatment outcomes than did those who had never used heroin (Weiss et al., 2011). However, the findings of the current secondary analysis show similar outcomes for patients who had never used heroin and for patients with lifetime heroin use who were adherent and thus received an adequate amount of additional drug counseling; heroin users who did not receive sufficient counseling, either because they were adherent but not randomized to the counseling condition or because they chose not to regularly attend the additional drug counseling they were offered, were most likely to be unsuccessful in treatment. This raises two key questions: what is it about heroin use that was associated with (1) worse outcomes overall for prescription-opioid dependent patients, and (2) equivalent outcomes to those of non-heroin users in patients who were adherent to treatment and thus received adequate exposure to additional drug counseling?

There is considerable underlying heterogeneity among patients with substance use disorders (Kuramoto et al., 2011): certain subtypes respond to particular treatments (Chamorro et al., 2012). In the current study, heterogeneity associated with only one indicator of severity, a history of heroin use, was correlated with treatment response. This finding supports results of studies that have found heroin-dependent patients to have worse treatment outcomes than prescription opioid-dependent patients (Moore et al., 2007; Potter et al., 2013). However, it is notable that heroin use was minimal among the participants in the present study who had used heroin, as individuals were excluded from the main study if they had used heroin on 4 or more days in the past month, had ever injected heroin, or had ever met criteria for opioid dependence based on heroin use alone (Weiss et al., 2010). Thus, even among those with a limited history of heroin use, this variable was most predictive of overall outcome and response to counseling.

One characteristic of heroin that may contribute to its status as an indicator of poor prognosis is its perceived dangerousness. Heroin is commonly viewed as the most harmful

of all drugs of abuse, and certainly as more risky than prescription opioids (Johnston et al., 2013; Lord et al., 2011). Thus, those with a history of heroin use have chosen to use a drug commonly accepted to be very dangerous. This type of behavior, which risks adverse health consequences, has been shown in other instances (e.g., with injection use) to be associated with poor treatment outcome (Potter et al., 2013). To the extent that a history of heroin use can be considered a marker of severity among patients (by virtue of its correlation with poor outcome overall), the results of the current study support previous research suggesting that more severe drug dependent patients respond better to more intensive forms of treatment (e.g., Tiet et al., 2007). However, merely being offered counseling in our trial was not sufficient to produce successful outcomes for the heroin users. Rather, these participants had to attend counseling sessions regularly to achieve outcomes similar to those of non-heroin users. As such, the results of the current study underline the importance of treatment adherence in producing benefit from an intervention, the significance of which has been demonstrated in trials of both pharmacologic (Oslin et al., 2008; Zweben et al., 2008) and psychosocial (Lydecker et al., 2010) treatments. In our study, level of exposure to counseling could not be disentangled from treatment adherence. However, it is noteworthy that adherence alone could not explain our findings. Adherence and thus adequate exposure to counseling did not correlate with better outcomes in non-heroin users, and adherent heroin users assigned to SMM alone had significantly worse outcomes than adherent heroin users receiving SMM plus additional ODC.

Of course, one cannot conclude that the association between good counseling attendance among heroin users and successful outcome implies that attending counseling leads to a good outcome. Indeed, a limitation of this study is the fact that individuals who attended more than 60% of treatment sessions, particularly if they were assigned to SMM+ODC, were a self-selected group, and were not, of course, randomly assigned to be adherent to treatment. The study is also limited by the fact that SMM sessions were delivered weekly, which is more frequent than general community practice (Arfken et al., 2010). Thus, one might expect a ceiling effect for the combination of buprenorphine-naloxone and SMM, making it more difficult for additional drug counseling to improve outcomes in the non-heroin users.

The notably poor outcomes among the heroin users, however, and the significant difference in outcome for adherent heroin users who were assigned to additional drug counseling versus those assigned to standard medical management alone, suggest that patients with prescription opioid dependence are a heterogeneous group, with different treatment strategies appropriate for different subgroups. Future studies seeking to optimize treatment outcomes for prescription opioid dependent patients might focus on specific subgroups, including those with a history of heroin use. Some recent pharmacotherapy research in alcohol-dependent populations has been designed to test prospectively for such heterogeneity, e.g., randomizing by genotype; three studies (Anton et al., 2008; Johnson et al., 2011; Kranzler et al., 2014) have demonstrated that specific genetic subgroups of alcohol-dependent patients may respond successfully to particular medications. To the extent that we can determine meaningful subgroups of opioid-dependent patients who respond to different behavioral treatments, we might be able to similarly design studies that

can move behavioral treatments as well as medications toward a goal of “personalized medicine.”

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Table 1

Likelihood of successful opioid use outcomes at Phase 2, weeks 9-12[a]

Table 1a. All participants (N=360)

	OR	95% CI	p value
Main effects			
Heroin	2.0	1.3-3.3	**.004**
Chronic pain	1.3	0.8-2.0	.240
Drug severity	2.9	0.2-58.2	.484
Interaction with Phase 2 treatment			
Heroin	1.6	0.6-4.2	.342
Chronic pain	0.6	0.2-1.4	.218
Drug severity	0.2	0.0-76.8	.585

Table 1b. Participants with adequate adherence to treatment (n=266)

	OR	95% CI	p value
Main effect of Phase 2 treatment	0.7	0.4-1.1	.107
Interaction with Phase 2 treatment			
Heroin	3.7	1.1-11.8	**.03**
Chronic pain	0.5	0.2-1.5	.213
Drug severity	1.5	0.001-4023.5	.915

[a] All models were adjusted for Phase 1 treatment condition.